

2/17/05

L4 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

AB A method for recovering a weak organic acid (such as a low-mol.-weight alc.) from a fermentation broth or other aqueous solution containing ≤40% by volume of the

organic acid comprises dissolving a base or a basic salt of an acid having a pKa >6 in the fermentation broth in an amount of ≥ 26 g/100 mL solution This results in a 2-phase system comprising a lower phase rich in base (or basic salt) and an upper phase rich in the weak organic acid. The organic acid is then recovered from the upper phase. The method is particularly useful for the recovery of EtOH from fermented biomass, for example in an integrated EtOH-water separation/fermentation

effluent

waste treatment process.

AN 1986:459475 CAPLUS

DN 105:59475

TI Recovery of a weak organic acid from its aqueous solution

IN Reeves, Russell Robert

PA Apace Research Ltd., Australia

SO Eur. Pat. Appl., 18 pp.

CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	EP 173544	A2	19860305	EP 1985-305942	19850821
	EP 173544	A3	19860521		
	EP 173544	B1	19910522		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
				AU 1984-6711	A 19840822
	AU 8545938	A1	19860227	AU 1985-45938	19840822
	AU 576377	B2	19880825		
				AU 1984-6711	A 19840822
	US 4594466	A	19860610	US 1985-761482	19850801
				AU 1984-6711	A 19840822
	IN 165111	A	19890819	IN 1985-MA602	19850802
				AU 1984-6711	A 19840822
	BR 8504008	A	19860610	BR 1985-4008	19850821
				AU 1984-6711	A 19840822
	CA 1241025	A1	19880823	CA 1985-489142	19850821
				AU 1984-6711	A 19840822
	AT 63739	E	19910615	AT 1985-305942	19850821
				AU 1984-6711	A 19840822
				EP 1985-305942	A 19850821

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NEWS	9	DEC 17	ELCOM reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	10	DEC 17	COMPUAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	11	DEC 17	SOLIDSTATE reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	12	DEC 17	CERAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	13	DEC 17	THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
NEWS	14	DEC 30	EPFULL: New patent full text database to be available on STN
NEWS	15	DEC 30	CAPLUS - PATENT COVERAGE EXPANDED
NEWS	16	JAN 03	No connect-hour charges in EPFULL during January and February 2005
NEWS	17	JAN 26	CA/CAPLUS - Expanded patent coverage to include the Russian Agency for Patents and Trademarks (ROSPATENT)
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NEWS	19	FEB 16	STN User Update to be held in conjunction with the 229th ACS National Meeting on March 13, 2005
NEWS EXPRESS			JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005
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STRUCTURE FILE UPDATES: 15 FEB 2005 HIGHEST RN 831913-30-5

DICTIONARY FILE UPDATES: 15 FEB 2005 HIGHEST RN 831913-30-5

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<http://www.cas.org/ONLINE/DBSS/registryss.html>

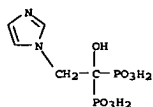
=> s zoledronic

L1 2 ZOLEDRONIC

=> d 1-2

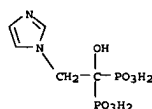
2/17/05

L1 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN
RN 165800-06-6 REGISTRY
CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis-,
monohydrate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Zoledronic acid hydrate
MF C5 H10 N2 O7 P2 . H2 O
SR US Adopted Names Council (USAN)
LC STN Files: BIOTECHNO, CA, CAPLUS, CENB, CHEMCATS, CIN, EMBASE, IPA,
MRCK*, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
DT.CA Caplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC
(Process); PRP (Properties); USES (Uses)
CRN (118072-93-8)



1 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN
RN 118072-93-8 REGISTRY
CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
(CA INDEX NAME)
OTHER NAMES:
CN (1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid
CN 1-Hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid
CN CGP 42446
CN Zoledronate
CN Zoledronic acid
CN Zomea
FS 3D CONCORD
MF C5 H10 N2 O7 P2
CI CCM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,
CANCERLIT, CAPLUS, CASREACT, CEN, CHEMCATS, CIN, CSCHM, DDPU,
DIOGENES,
DRUGU, EMBASE, IMSDRUGNEWS, IMPATENTS, IMSRESEARCH, IPA, MEDLINE,
MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USPAT2,
USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
DT.CA Caplus document type: Book; Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC
(Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical
study); BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
study); PREP (Preparation); PROC (Process); PRP (Properties); USES
(Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

334 REFERENCES IN FILE CA (1907 TO DATE)
17 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
343 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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2/17/05

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

9.14

9.35

FILE 'CAPLUS' ENTERED AT 14:47:03 ON 17 FEB 2005

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FILE COVERS 1907 - 17 Feb 2005 VOL 142 ISS 8

FILE LAST UPDATED: 16 Feb 2005 (20050216/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l1/p

L2 14 L1/P

=> d abs fbib hitstr 1-14

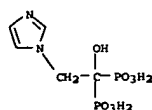
2/17/05

L2 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2005 ACS ON STN
AB The invention relates to polymorphs of zoledronic acid and zoledronate sodium salts, amorphous zoledronate sodium salts, processes for making the polymorphs and amorphous zoledronate sodium salt and pharmaceutical compns. containing the polymorphs and amorphous zoledronate sodium salt.
For example, zoledronic acid crystal Form I was prepared by a phosphorylation reaction of 1-imidazoleacetic acid in the presence of phosphorous acid and phosphorus oxychloride in silicon oil as a diluent.
AN 2005:58222 CAPLUS
TI Processes for preparation of crystal forms of zoledronic acid and zoledronate sodium salts
IN Aronhime, Judith; Lifshitz-Liron, Revital
PA Teva Pharmaceutical Industries, Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

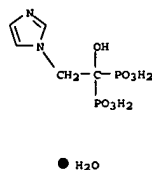
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005005447	A2	20050120	WO 2004-US21626	20040706
M:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, GU, HD, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, ME, MG, MK, MN, MW, MX, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW,			
RM:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

IT 118072-93-8P, Zoledronic acid
RL: PEP (Physical, engineering or chemical process); PRP (Properties);
PYP (Physical process); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(preparation of crystal forms of zoledronic acid and amorphous and crystal forms of zoledronate sodium salts for dosage forms)
RN 118072-93-8 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
(CA INDEX NAME)

L2 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2005 ACS ON STN (Continued)



IT 165800-06-6P
RL: PEP (Physical, engineering or chemical process); PRP (Properties);
PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of crystal forms of zoledronic acid and amorphous and crystal forms of zoledronate sodium salts for dosage forms)
RN 165800-06-6 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis-, monohydrate (9CI) (CA INDEX NAME)

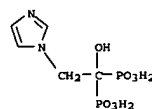


L2 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2005 ACS ON STN
AB The invention relates to processes for preparing and purifying zoledronic acid. Zoledronic acid was suspended in water at room temperature. The pH of the suspension was adjusted to 14 by adding sodium hydroxide to obtain a clear solution. Then the pH of the solution was adjusted to 1 by adding 32% HCl. The solution was cooled to 50° and was stirred at this temperature for 2.5 h. A massive precipitate of zoledronic acid was observed at 20°. The product was then isolated by filtration, washed with water and dried in a vacuum oven at 50° for 1.5 h and then in a vented oven at 65° for 24 h to obtain recrystallized zoledronic acid.
AN 2004:740139 CAPLUS
DN 141:243686
TI Process for purification of zoledronic acid
IN Lifshitz-Liron, Revital; Lidor-Hadas, Remy
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 7 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004075860	A2	20040910	WO 2004-US5865	20040227
M:	AE, AG, AL, AM, AN, AT, AU, AZ, BA, BB, BG, BR, BR, BW, BY, BZ, CA, CH, CN, CO, CO, CR, CU, CU, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, GR, GR, GU, HD, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, ME, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI			
RM:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2004230076	A1	20041118	US 2003-449837P	P 20030227
			US 2004-789821	20040227
			US 2003-449837P	P 20030227

IT 118072-93-8P, Zoledronic acid
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(process for purification of zoledronic acid via reaction with sodium hydroxide and acidification with hydrochloric acid)
RN 118072-93-8 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
(CA INDEX NAME)

L2 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2005 ACS ON STN (Continued)



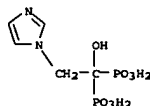
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L2 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB The effects of a series of 102 bisphosphonates on the inhibition of growth of *Entamoeba histolytica* and *Plasmodium falciparum* in vitro have been determined, and selected compds. were further investigated for their in vivo activity. Forty-seven compds. tested were active (IC50 < 200 µM) vs. *E. histolytica* growth in vitro. The most active compds. (IC50 .apprx. 4-9 µM) were nitrogen-containing bisphosphonates with relatively large aromatic side chains. Simple n-alkyl-1-hydroxy-1,1-bisphosphonates, known inhibitors of the enzyme farnesylpyrophosphate (FPP) synthase, were also active, with optimal activity being found with C9-C10 side chains. However, numerous other nitrogen-containing bisphosphonates known to be potent FPP synthase inhibitors, such as risedronate or pamidronate, had little or no activity. Several pyridine-derived bisphosphonates were quite active (IC50 .apprx. 10-20 µM), and this activity was shown to correlate with the basicity of the aromatic group, with activity decreasing with increasing pKa values. The activities of all compds. were tested vs. a human nasopharyngeal carcinoma (KB) cell line to enable an estimate of the therapeutic index (TI). Five bisphosphonates were selected and then screened for their ability to delay the development of amebic liver abscess formation in an *E. histolytica* infected hamster model. Two compds. were found to decrease liver abscess formation at 10 mg/kg i.p. with little or no effect on normal liver mass. With *P. falciparum*, 35 compds. had IC50 values <200 µM in an in vitro assay. The most active compds. were also simple n-alkyl-1-hydroxy-1,1-bisphosphonates, having IC50 values around 1 µM. Five compds. were again selected for in vivo investigation in a *Plasmodium berghei* ANKA BALB/c mouse suppressive test. The most active compound, a C9 n-alkyl side chain containing bisphosphonate, caused an 80% reduction in parasitemia with no overt toxicity. Taken together, these results show that bisphosphonates appear to be useful lead compds. for the development of novel antiamebic and antimalarial drugs.

AN 2003:961354 CAPLUS
 DN 140:138740
 TI Effects of Bisphosphonates on the Growth of *Entamoeba histolytica* and *Plasmodium* Species in Vitro and in Vivo
 AU Ghosh, Subhash; Chen, Jullen M. W.; Lee, Christopher R.; Meints, Gary A.; Lewis, Jared C.; Tovian, Zev S.; Plessner, Ryan M.; Loftus, Timothy C.; Bruchhaus, Iris; Kendrick, Howard; Croft, Simon L.; Kemp, Robert G.; Kobayashi, Seiki; Nozaki, Tomoyoshi; Oldfield, Eric
 CS Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA
 SO Journal of Medicinal Chemistry (2004), 47(1), 175-187
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 IT 118072-93-8P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

L2 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. and structure-activity relationship studies of bisphosphonates on growth of *Entamoeba histolytica* and *Plasmodium* species in vitro and in vivo)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)



RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB Provided is a novel method of making bisphosphonic acids, e.g. risedronic acid, including the step of combining a carboxylic acid, phosphorous acid, and a halophosphorous compound in the presence of a diluent that is an aromatic hydrocarbon or a silicone fluid. When the diluent is an aromatic hydrocarbon, a inert support or ortho-phosphoric acid codiluent is advantageously included. Thus, reaction of 3-pyridineacetic acid hydrochloride with phosphorous acid in PhMe containing silicone fluid followed by treatment with phosphorous oxychloride and workup gave risedronic acid monohydrate.

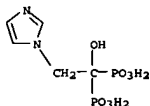
AN 2003:931375 CAPLUS
 DN 139:381614
 TI Use of certain diluents for making bisphosphonic acids
 IN Lidor-Hadas, Rami; Harel, Zvi; Lifshitz-Liron, Revital; Kovalevski-Liron, Eli
 PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
 SO PCT Int. Appl., 37 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003097655	A1	20031127	WO 2003-US15676	20030519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CP, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004043967	A1	20040304	US 2002-381284P	P 20020517
			US 2002-401313P	P 20020806
			US 2002-423337P	P 20021101
			US 2002-431838P	P 20021209
			US 2003-450193P	P 20030225
EP 1476451	A1	20041117	EP 2003-729005	20030519
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			US 2002-381284P	P 20020517
			US 2002-401313P	P 20020806
			US 2002-423337P	P 20021101
			US 2002-431838P	P 20021209
			US 2003-450193P	P 20030225
			WO 2003-US15676	W 20030519

OS CASREACT 139:381614
 IT 118072-93-8P, Zoledronic acid

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L2 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (use of arom. hydrocarbon diluents in phosphorylation of carboxylic acid for prepn. of bisphosphonic acids)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

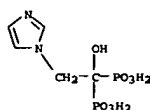
2/17/05

L2 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB A process for preparing bisphosphonic acids,
 (M10) (M20) P(O)(C(R1)(OH)F(O)(OH)₂)
 (OH) (M1-M4 = H, monovalent cation; R1 = Me, 2-(1-imidazolyl)methyl,
 3-pyridylmethyl, 2-imidazo[1,2-a]pyridylmethyl, H₂N(CH₂)_n, n = 2-5,
 MeN(CH₂)₂CH₂, n-PrN(Me)(CH₂)₅, etc.), characterized in that the reaction of
 synthesis is conducted in a reaction consisting of bisphosphonic acids,
 is described. Thus, reaction of γ-aminobutyric acid with PCl₃ in the
 presence of tributylammonium chloride (preparation given), aqueous NaOH,
 and usual
 workup gave 31% sodium alendronate.
 AN 2003:892788 CAPLUS
 DN 139:365070
 TI Preparation of bisphosphonic acids and salts thereof
 IN De Ferra, Lorenzo; Turchetta, Stefano; Massardo, Pietro; Casellato, Paolo
 PA Chemi S.p.A., Italy
 SO PCT Int. Appl., 13 pp.
 CODEN: PIXXDX
 DT Patent
 LA English
 PAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093282	A1	20031113	WO 2002-1B4941	20021125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1504012	A1	20050209	EP 2002-807339	20021125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
IT 2002-MI908 A 20020429				
WO 2002-1B4941 W 20021125				

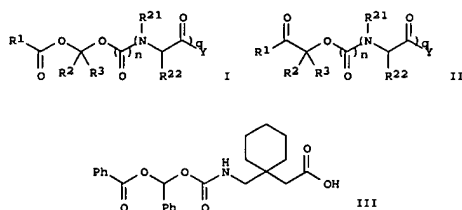
OS CASREACT 139:365070; MARPAT 139:365070
 IT 118072-93-8P, Zoledronic acid
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of bisphosphonic acids and their pharmacol. active salts)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)

L2 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 Q1



AB The present invention provides a method for synthesizing 1-(acyloxy)alkyl
 deriva. I from 1-acyloxyalkyl deriva. II [wherein n = 0-1; q = 0-1; provided
 that n and q = 0 unless Y = NRR' or OR; Y = NRR', OR, COR, PO(OR')R, or
 PO(OR') (OR); NRR', OR, COR, PO(OR')R, or PO(OR') (OR) = groups derived
 from
 or drugs containing the indicated functional groups, with provisos: R1 = H
 or (un)substituted alkyl, (hetero)cycloalkyl, (hetero)arylalkyl, or a C23
 bile acid moiety; R2 and R3 = independently H or (un)substituted
 (cyclo)alkyl, (cyclo)alkoxycarbonyl, aryl(alkyl), carbamoyl, or
 heteroaryl(alkyl); or R1 and either R2 or R3 may join together with the
 atoms to which they are attached to form an (un)substituted
 (hetero)cycloalkyl ring optionally fused to a (hetero)aryl or
 (hetero)cycloalkyl ring; or CR2R3 = (un)substituted (hetero)cycloalkyl;
 R21 = independently H or (un)substituted alkyl; R22 = independently H or
 (un)substituted (cyclo)alkyl, alkoxy(carbonyl), acyl, alkylamino,
 alkylthio, carbamoyl, aryl(alkyl), heteroaryl(alkyl), etc.; or
 pharmaceutically acceptable salts, hydrates, or solvates thereof]. The
 method typically proceeds stereospecifically, in high yield, does not
 require the use of activated intermediates and/or toxic compds., and is
 readily amenable to scale-up. The invention also provides 1-acyloxyalkyl
 deriva. of known drug compds. and methods for synthesizing these
 1-acyloxyalkyl deriva. I and compns. thereof are useful as prodrugs (no
 data). For example, coupling of benzoin with p-nitrophenyl chloroformate
 using DMAP in CH₂Cl₂, followed by the addition of gabapentin in the
 presence
 of TEA and TMSCl CH₂Cl₂ gave 1-[(α-benzoylbenzyloxy)carbonyl]aminom
 ethyl-1-cyclohexanecarboxylic acid (90% over two steps). Oxidation with
 mCPBA
 in CH₂Cl₂ provided the α-(benzyloxy)benzyl carbamate III (47%).
 AN 2003:717749 CAPLUS
 DN 139:245676
 TI Methods for synthesis of 1-(acyloxy)alkyl carbamates and analogs as
 prodrugs from 1-acyloxyalkyl derivatives and compositions thereof
 IN Gallop, Mark A.; Xiang, Jia-Ning; Yao, Fenmei; Bhat, Lexminarayan; Zhou,
 Cindy X.

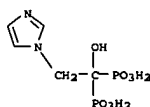
10789821

L2 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PA USA
 SO U.S. Pat. Appl. Publ., 34 pp.
 CODEN: USXXCO
 DT Patent
 LA English
 PAN.CNT 1

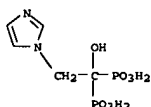
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003171303	A1	20030911	US 2002-167797	20020611
US 2002-358603P P 20020219				
US 2002-371535P P 20020409				
WO 2003077902	A1	20030925	WO 2002-US18691	20020611
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
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US 2002-358603P P 20020219				
US 2002-371535P P 20020409				
EP 1485082	A1	20041215	EP 2002-746514	20020611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002-358603P P 20020219				
US 2002-371535P P 20020409				
WO 2002-US18691 W 20020611				

OS CASREACT 139:245676; MARPAT 139:245676
 IT 118072-93-8DP, Zoledronate, prodrug derivative
 RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of alkoxyalkyl carbamates and analogs as prodrugs by
 oxidation of
 acylalkyl deriva.)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)

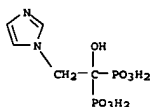


2/17/05

L2 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB Stirring imidazole with Et bromoacetate in MeCN in the presence of
 KF/AlCl₃ at 30° for 3 h gave 77.5% 1H-imidazole-1-acetic acid Et
 ester, which was refluxed with water for 7 h to give
 1H-imidazole-1-acetic
 acid (I). Treating I with PCl₃ and 85% H₃PO₄ in the presence of PEG-400
 at 75° for 4 h gave 50.7% zoledronic acid.
 AN 2003:159671 CAPLUS
 DN 139:381537
 TI Synthesis of zoledronic acid
 AU Zhu, Ju; Zhou, You-jun; Li, Jia-guo; Liu, Jian-fei; Zhang, Wan-nian
 CS Dept. of Medicinal Chemistry, College of Pharmacy, Second Military Med.
 Univ., Shanghai, 200433, Peop. Rep. China
 SO Zhongguo Xinyao Zazhi (2003), 12(1), 39-40
 CODEN: ZXZHA6; ISSN: 1003-3734
 PB Zhongguo Xinyao Zazhishe
 DT Journal
 LA Chinese
 OS CASREACT 139:381537
 IT 118072-93-8P, Zoledronic acid
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (synthesis of zoledronic acid)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)

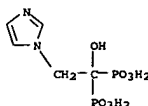


L2 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB A review covering the 24 new drugs approved by the Food and Drug
 Administration in the year 2001. Therapeutics are grouped according to
 the following coded areas: (A) agents affecting neurotransmitters and
 cytokines, (B) antiinflammatory agents, (C) hormone related agents, (D)
 anti-infectious agents, and (E) miscellaneous agents. A synopsis for
 each drug
 includes a brief description of its medical utility, a mechanism of
 action
 if known, a chemical structure, and a pathway for its synthesis.
 AN 2002:720795 CAPLUS
 DN 138:280580
 TI FDA new drug approvals in 2001
 AU Zhao, Kang; He, Lan; Reiner, John
 CS The College of Pharmaceuticals and Biotechnology, Tianjin University,
 Peop. Rep. China
 SO Frontiers of Biotechnology & Pharmaceuticals (2002), 3, 400-413
 CODEN: FBPRBL
 PB Science Press New York Ltd.
 DT Journal, General Review
 LA English
 IT 118072-93-8P, Zoledronic acid
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN
 (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);
 PREP (Preparation); USES (Uses)
 (FDA new drug approvals in 2001)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB Title compound, a new drug for treating hypercalcemia, was synthesized
 via
 substitution imidazole with Et bromoacetate, after hydrolyzation to
 afford
 imidazol-1-ylacetic acid, then reacted with phosphoric acid with the
 presence of phosphorus trichloride, giving the product with overall yield
 27.0%. By using TEBA instead of BBDE chloride as phase transfer
 catalyst,
 and imidazole acetic acid instead of its HCl salt as the key
 intermediate,
 this process can easily obtain the product in good quality and yield.
 AN 2003:30096 CAPLUS
 DN 139:69193
 TI Improved process for the synthesis of zoledronic acid as a new drug for
 treating hypercalcemia
 AU Li, Jiaming; Tong, Yuanfeng; Zhang, Yong
 CS Department of Pharmaceutical Chemistry, Anhui College of Traditional
 Chinese Medicine, Hefei, 230038, Peop. Rep. China
 SO Zhongguo Yaowu Huaxue Zazhi (2003), 12(3), 164-165, 186
 CODEN: ZYHZEJ; ISSN: 1005-0108
 PB Zhongguo Yaowu Huaxue Zazhi Bianjibu
 DT Journal
 LA Chinese
 OS CASREACT 139:69193
 IT 118072-93-8P, Zoledronic acid
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)
 (Improved process for the synthesis of zoledronic acid)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)

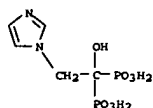


L2 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB Bisphosphonates (BPs) are pyrophosphate analogs in which the oxygen in
 P-O-P has been replaced by a carbon, resulting in a metabolically stable
 P-C-P structure. Pamidronate (1b, Novartis), a second-generation BP, was
 the starting point for extensive SAR studies. Small changes of the
 structure of pamidronate lead to marked improvements of the inhibition of
 osteoclastic resorption potency. Alendronate (1c, MSD), with an extra
 methylene group in the N-alkyl chain, and olpadronate (1h, Gador), the
 N,N-di-Me analog, are about 10 times more potent than pamidronate.
 Extending one of the N-Me groups of olpadronate to a pentyl substituent
 leads to ibandronate (1k, Roche, Boehringer-Mannheim), which is the most
 potent close analog of pamidronate. Even slightly better antiresorptive
 potency is achieved with derivs. having a Ph group linked via a short
 aliphatic tether of three to four atoms to nitrogen, the second
 substituent
 being preferentially a Me group (e.g., 4g, 4j, 5d, or 5r). The most
 potent BPs are found in the series containing a heteroatom moiety (with
 at
 least one nitrogen atom), which is linked via a single methylene group to the
 geminal bisphosphonate unit. Zoledronic acid (6i), the most potent
 derivative, has an ED50 of 0.07 mg/kg in the TPTX in vivo assay after
 a.c.
 administration. It not only shows by far the highest therapeutic ratio
 when comparing resorption inhibition with undesired inhibition of bone
 mineralization but also exhibits superior renal tolerability. Zoledronic
 acid (6i) has thus been selected for clin. development under the
 registered trade name Zometa. The results of the clin. trials indicate
 that low doses are both efficacious and safe for the treatment of
 tumor-induced hypercalcemia, Paget's disease of bone, osteolytic
 metastases, and postmenopausal osteoporosis.
 AN 2002:539062 CAPLUS
 DN 137:226194
 TI Highly Potent Geminal Bisphosphonates. From Pamidronate Disodium (Aredia)
 to Zoledronic Acid (Zometa)
 AU Widler, Leo; Jaeggli, Knut A.; Glatt, Markus; Mueller, Klaus; Bachmann,
 Rolf; Bisping, Michael; Born, Anne-Ruth; Cortesi, Reto; Guiglia,
 Gabriela;
 Jeker, Heidi; Klein, Remy; Ramseier, Ueli; Schmid, Johann; Schreiber,
 Gerard; Selteneimyer, Yves; Green, Jonathan R.
 CS Arthritis and Bone Metabolism Therapeutic Area, Novartis Pharma Research,
 Basel, CH-4002, Switz.
 SO Journal of Medicinal Chemistry (2002), 45(17), 3721-3738
 CODEN: JMCHAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 OS CASREACT 137:226194
 IT 118072-93-8P
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
 activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL
 (Biological study); PREP (Preparation); USES (Uses)
 (bisphosphonates preparation and structure-related bone antiresorptive
 properties)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)

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L2 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

AB Two new series of fused aza-heteroarylphosphonates which are structurally quite different from incadronate (YM175), and related compds.

were synthesized and evaluated for antiresorptive activity using a parathyroid hormone (PTH)-induced hypercalcemia model in rats (PIH model). Among these compds., several exhibited more potent antiresorptive activity

than pamidronate. In particular, [1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene]bisphosphonic acid (5b, minodronate) was 100-fold more potent than pamidronate in not only the PIH model, but also in an immobilization bone atrophy model in rats (DA model), and was selected

for clin. development. The structure-activity relations in these new series of bisphosphonates are discussed. X-ray crystal structures of [1-hydroxy-2-(imidazo[1,2-a]pyridin-2-yl)ethylidene]bisphosphonic acid (5a) (space group P21/c, $R_w = 0.063$, $Z = 4$) and 5b (space group P.hivin.1,

$R_w = 0.099$, $Z = 2$) were determined

AN 1998:758024 CAPLUS

DN 130:110331

TI Studies on novel bone resorption inhibitors. II. Synthesis and pharmacological activities of fused aza-heteroarylphosphonate derivatives

AU Takeuchi, Makoto; Sakamoto, Shuichi; Kawamuki, Kousei; Kurihara, Hiroyuki;

Nakahara, Hideaki; Isomura, Yasuo

CS Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, 305-8585, Japan

SO Chemical & Pharmaceutical Bulletin (1998), 46(11), 1703-1709

CODEN: CPBTAL; ISSN: 0009-2363

PB Pharmaceutical Society of Japan

DT Journal

LA English

OS CASREACT 130:110331

IT 118072-93-8P

RL: BAC (Biological activity or effector, except adverse); BSU

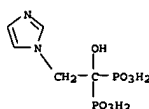
(Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (antiresorptive activity)

RN 118072-93-8 CAPLUS

CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis-

(CA

INDEX NAME)



L2 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

AB The azabisphosphonic acids R6R7NCR4R5(CR2R3)nCR1(PO3H2)2 [$n = 0, 1-6$; R1

=

H, OH, alkyl, alkoxy, halo, etc.; R2-5 H, (un)substituted hydrocarbyl, etc.; R6, R7 = R2, (un)substituted pyridyl or (un)substituted amino; R6R7N, R4R6CN or R2R6CN = (un)substituted N-containing heterocyclyl;

R2R4C and

R4R5C = (un)substituted carbocyclyl and their salts or hydrolyzable esters are prepared as postemergence herbicides.

AN 1998:186482 CAPLUS

DN 128:240717

TI Preparation of herbicidal azabisphosphonic acids

IN Fisher, Karl J.; Woolard, Frank X.; Leadbetter, Michael R.; Gerdes, John M.

PA Zeneca Ltd., UK

SO U.S., 43 pp., Cont.-in-part of U.S. Ser. No. 133,722, abandoned.

CODEN: USXXAM

DT Patent

LA English

PAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5728650	A	19980317	US 1995-418970	19950407
			US 1993-133722	B2 19931007
TW 401276	B	20000811	TW 1994-83109255	19941005
ZA 9407814	A	19950814	ZA 1994-7814	19941006
			US 1993-133722	A 19931007
IL 111180	A1	19990922	IL 1994-111180	19941006
			US 1993-133722	A 19931007
CA 2173607	AA	19950420	CA 1994-2173607	19941007
			US 1993-133722	A 19931007
CN 1134657	A	19961030	CN 1994-194096	19941007
			US 1993-133722	A 19931007
HU 74893	A2	19970228	HU 1996-839	19941007
			US 1993-133722	A 19931007
CA 2217655	AA	19961010	CA 1996-2217655	19960408
			US 1995-418970	A 19950407
WO 9631124	A1	19961010	WO 1996-US4869	19960408
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9654475	A1	19961023	AU 1995-418970	A 19950407
			AU 1996-54475	19960408
			US 1995-418970	A 19950407
			WO 1996-US4869	W 19960408
EP 820230	A1	19980128	EP 1996-911660	19960408
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			US 1995-418970	A 19950407
			WO 1996-US4869	W 19960408
CN 1181690	A	19980513	CN 1996-193132	19960408
			US 1995-418970	A 19950407
BR 9604975	A	19980609	BR 1996-4975	19960408
			US 1995-418970	A 19950407
			WO 1996-US4869	W 19960408
JP 11503429	T2	19990326	JP 1996-530540	19960408

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2/17/05

L2 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
 FAN 1995:750617
 PATENT NO. KIND DATE APPLICATION NO. DATE
 PI WO 9510188 A2 19950420 WO 1994-GB2183 19941007
 WO 9510188 A3 19950504
 M: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, RM: KE, MM, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

PATENT FAMILY INFORMATION:

US 1995-418970 A 19950407
 WO 1996-US4869 W 19960408
 NO 1997-4619 19971006
 US 1995-418970 A 19950407
 WO 1996-US4869 W 19960408

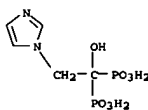
US 1993-133722 A 19931007
 TM 1994-83109255 19941005
 US 1993-133722 A 19931007
 ZA 1994-7814 19941006
 US 1993-133722 A 19931007
 IL 1994-111180 19941006
 US 1993-133722 A 19931007
 CA 1994-2173607 19941007
 US 1993-133722 A 19931007
 AU 1994-77901 19941007
 US 1993-133722 A 19931007
 WO 1994-GB2183 W 19941007
 EP 1994-928482 19941007
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

US 1993-133722 A 19931007
 WO 1994-GB2183 W 19941007
 CN 1994-194096 19941007
 US 1993-133722 A 19931007
 HU 1996-839 19941007
 US 1993-133722 A 19931007
 BR 1994-7762 19941007
 US 1993-133722 A 19931007
 WO 1994-GB2183 W 19941007
 JP 1994-511442 19941007
 US 1993-133722 A 19931007
 WO 1994-GB2183 W 19941007
 NO 1996-1389 19960403
 US 1993-133722 A 19931007
 WO 1994-GB2183 W 19941007
 FI 1996-1520 19960404
 US 1993-133722 A 19931007
 WO 1994-GB2183 W 19941007

FAN 1996:705780
 PATENT NO. KIND DATE APPLICATION NO. DATE
 PI WO 9631124 A1 19961010 WO 1996-US4869 19960408

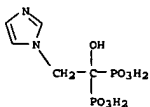
L2 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
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 US 1993-133722 B2 19931007
 AU 1996-54475 19960408
 US 1995-418970 A 19950407
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 EP 1996-911660 19960408
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 US 1995-418970 A 19950407
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 BR 1996-4975 19960408
 US 1995-418970 A 19950407
 WO 1996-US4869 W 19960408
 JP 1996-530540 19960408
 US 1995-418970 A 19950407
 WO 1996-US4869 W 19960408
 NO 1997-4619 19971006
 US 1995-418970 A 19950407
 WO 1996-US4869 W 19960408

OS MARPAT 128:240717
 IT 118072-93-8P
 RL: AGR (Agricultural use); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (Preparation as herbicide)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB Moderate to poor yields of 1-hydroxy-1,1-bisphosphonates, prepared by reacting a carboxylic acid with PCl3 and H3PO4, can be substantially increased by running the reaction in methanesulfonic acid. The target compds. thus prepared are (3-amino-1-hydroxypropylidene)bis(phosphonic acid), (4-amino-1-hydroxybutylidene)bis(phosphonic acid), etc., and alendronate sodium.
 AN 1995:947515 CAPLUS
 DN 124:117423
 TI Preparation of (4-Amino-1-Hydroxybutylidene)bisphosphonic Acid Sodium Salt, MK-217 (Alendronate Sodium). An Improved Procedure for the Preparation of 1-Hydroxy-1,1-bisphosphonic Acids
 AU Kieczkowski, Gerard R.; Jobson, Ronald B.; Melillo, David G.; Reinhold, Donald F.; Grenda, Victor J.; Shinkai, Ichiro
 CS Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065, USA
 SO Journal of Organic Chemistry (1995), 60(25), 8310-12
 CODEN: JOCEAH; ISSN: 0022-3263
 PB American Chemical Society
 DT Journal
 LA English
 OS CASREACT 124:117423
 IT 118072-93-8P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (Preparation of (aminohydroxybutylidene)bisphosphonates)
 RN 118072-93-8 CAPLUS
 CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
 (CA INDEX NAME)



L2 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
 AB RICH2CR2(PO3H2)2 (I; R1 = 5-membered heteroaryl comprising 2-4 N atoms or 1-2 N atoms plus an O or S atom with optional substituents; R2 = H, OH, NH2, alkylthio, halo) and their salts, useful as pharmaceuticals, are prepared. PCl3 was added to a mixture of 0.053 mol imidazol-4-ylacetic acid
 HCl in 85% H3PO4 and PhCl at 100° to give 40% title acid I (R1 = imidazol-4-yl, R2 = OH) (II). A tablet formulation was prepared from II.2Na
 100.0, lactose 100.0, corn starch 47.0, and Mg stearate 3.0 g.
 AN 1989:24084 CAPLUS
 DN 110:24084
 TI Preparation of alkylenediphosphonic acids and salts, and pharmaceutical compositions containing them
 PA Ciba-Geigy A.-G., Switz.
 SO Jpn. Kokai Tokkyo Koho, 17 pp.
 CODEN: JKKKAF
 DT Patent
 LA Japanese
 FAN.CNT 2

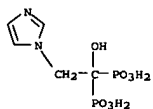
PATENT NO. KIND DATE APPLICATION NO. DATE
 PI JP 63150291 A2 19880622 JP 1987-292198 19871120
 JP 2744238 B2 19980428
 EP 275821 A1 19880727 CH 1986-4666 A 19861121
 EP 275821 B1 19920226 EP 1987-810664 19871116
 R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
 AT 72816 E 19920315 AT 1987-810664 A 19871116
 CH 1986-4666 A 19861121
 CH 1986-4666 A 19871116
 ES 2038692 T3 19930801 EP 1987-810664 A 19871116
 IL 84497 A1 19941021 CH 1986-4666 A 19861121
 IL 1987-84497 19871116
 CH 1986-4666 A 19861121
 FI 8705096 A 19880522 FI 1987-5096 19871118
 FI 87570 B 19921015
 FI 87570 C 19931215
 CA 1338937 A1 19970225 CH 1986-4666 A 19861121
 CA 1987-552209 19871119
 CH 1986-4666 A 19861121
 DK 8706095 A 19880522 DK 1987-6095 19871120
 DK 174098 B1 20020617
 CH 1986-4666 A 19861121
 NO 8704856 A 19880524 NO 1987-4856 19871120
 NO 173446 B 19930506
 NO 173446 C 19931215
 AU 8781453 A1 19880526 AU 1987-81453 19871120
 AU 607722 B2 19910314
 ZA 8708698 A 19880727 CH 1986-4666 A 19861121
 ZA 1987-8698 19871120
 CH 1986-4666 A 19861121
 HU 46330 A2 19881028 HU 1987-5160 19871120
 HU 1990150 B 19900129
 CH 1986-4666 A 19861121
 DD 270533 A5 19890802 DD 1987-309267 19871120
 CH 1986-4666 A 19861121

PATENT FAMILY INFORMATION:

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2/17/05

L2 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
FAN 1991:62355
PATENT NO. KIND DATE APPLICATION NO. DATE
PI US 4939130 A 19900703 US 1989-315962 19890227
CH 1986-4666 A 19861121
US 1987-120284 B2 19871113
AT 72816 E 19920315 AT 1987-810664 19871116
CH 1986-4666 A 19861121
EP 1987-810664 A 19871116
OS MARPAT 110:24084
IT 118072-93-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as calcium metabolism regulator)
RN 118072-93-8 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
(CA INDEX NAME)



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2/17/05

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=> s purification and ph
    304806 PURIFICATION
      945 PURIFICATIONS
    305453 PURIFICATION
          (PURIFICATION OR PURIFICATIONS)
    274930 PURIFN
      236 PURIFNS
    275033 PURIFN
          (PURIFN OR PURIFNS)
    449844 PURIFICATION
          (PURIFICATION OR PURIFN)
    1217033 PH
      9244 PHS
    1221098 PH
          (PH OR PHS)
L3      65924 PURIFICATION AND PH
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=> s purifying by changing pH
    31268 PURIFYING
    120733 CHANGING
      19 CHANGINGS
    120749 CHANGING
          (CHANGING OR CHANGINGS)
    1217033 PH
      9244 PHS
    1221098 PH
          (PH OR PHS)
L4      0 PURIFYING BY CHANGING PH
          (PURIFYING (1W) CHANGING (W) PH)
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=> s purif? by changing pH
    759574 PURIF?
    120733 CHANGING
      19 CHANGINGS
    120749 CHANGING
          (CHANGING OR CHANGINGS)
    1217033 PH
      9244 PHS
    1221098 PH
          (PH OR PHS)
L5      1 PURIF? BY CHANGING PH
          (PURIF? (1W) CHANGING (W) PH)
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=> d abs fbib hitstr
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2/17/05

LS ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
AB The apparatus includes a section for introducing the water to be treated, a section having a plurality of filtering materials (e.g., barite, limestone) for purification and changing pH, and a section for discharging the treated water.
AN 1996:664500 CAPLUS
DN 125:283963
TI Apparatus for purification of wastewater and water in natural area by filtration
IN Tezuka, Koichi; Mizumori, Takashi; Takagi, Takeo; Yoda, Hiroaki; Okajima, Hiroaki
PA Hitachi Ltd, Japan; Hitachi Tsuchiura Eng
SO Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKKXAF
DT Patent
LA Japanese
FAN CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 08206674	A2	19960813	JP 1995-14931	19950201
				JP 1995-14931	19950201

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=> s l2 and purif? and pH

759574 PURIF?

1217033 PH

9244 PHS

1221098 PH

(PH OR PHS)

L6 1 L2 AND PURIF? AND PH

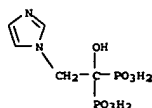
=> d abs fbib hitstr

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2/17/05

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
AB The invention relates to processes for preparing and purifying
zoledronic acid. Zoledronic acid was suspended in water at room
temperature
The pH of the suspension was adjusted to 14 by adding sodium
hydroxide to obtain a clear solution. Then the pH of the solution was
adjusted to 1 by adding 32% HCl. The solution was cooled to 50° and
was stirred at this temperature for 2.5 h. A massive precipitate of
zoledronic acid
was observed at 20°. The product was then isolated by filtration,
washed with water and dried in a vacuum oven at 50° for 1.5 h and
then in a vented oven at 65° for 24 h to obtain recrystd.
zoledronic acid.
AN 2004:740139 CAPLUS
DN 141:243686
TI Process for purification of zoledronic acid
IN Lifshitz-Liron, Revital; Lidor-Madas, Rami
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA,
Inc.
SO PCT Int. Appl., 7 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE
PI WO 2004075860 A2 20040910 WO 2004-US5865 20040227
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,
BO, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,
CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,
ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, KZ, LC,
LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,
MZ, MZ, NA, NI
RM: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CO, CI, CM, GA, GN,
GO, GW, ML, MR, NE, SN, TD, TO, BF, BJ, CF, CO, CI, CM, GA, GN,
GO, GW, ML, MR, NE, SN, TD, TO
US 2004230076 A1 20041118 US 2003-449837P P 20030227
US 2004-789821 20040227
US 2003-449837P P 20030227
IT 118072-93-8P, Zoledronic acid
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP
(Preparation)
(process for purification of zoledronic acid via reaction with
sodium hydroxide and acidification with hydrochloric acid)
RN 118072-93-8 CAPLUS
CN Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis- (9CI)
(CA INDEX NAME)

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



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=> s l3 and purif? and pH

759574 PURIF?

1217033 PH

9244 PHS

1221098 PH

(PH OR PHS)

L7 65924 L3 AND PURIF? AND PH

=> s l7 and purification by changing pH

304806 PURIFICATION

945 PURIFICATIONS

305453 PURIFICATION

(PURIFICATION OR PURIFICATIONS)

274930 PURIFN

236 PURIFNS

275033 PURIFN

(PURIFN OR PURIFNS)

449844 PURIFICATION

(PURIFICATION OR PURIFN)

120733 CHANGING

19 CHANGINGS

120749 CHANGING

(CHANGING OR CHANGINGS)

1217033 PH

9244 PHS

1221098 PH

(PH OR PHS)

1 PURIFICATION BY CHANGING PH

(PURIFICATION(1W)CHANGING(W)PH)

L8 1 L7 AND PURIFICATION BY CHANGING PH

=> d abs